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Immunogenicity of tick-borne encephalitis virus glycoprotein fragments: epitope-specific analysis of the antibody response.

Heinz FX, Tuma W, Guirakhoo F, Berger R, Kunz C.

After digestion with trypsin, alpha-chymotrypsin, or chemical cleavage using CNBr, fragments of the tick-borne encephalitis (TBE) virus glycoprotein were isolated which retained their reactivity with neutralizing monoclonal antibodies defining a denaturation-resistant antigenic domain. Upon immunization of mice, these fragments induced antibodies reactive with the immunizing peptide, the denatured glycoprotein and the native glycoprotein as a constituent of the whole virus. The immune sera revealed the same properties as the monoclonal antibodies that were used to select the fragments for immunization: neutralizing activity; haemagglutination-inhibiting activity; blocking of the binding of antibodies used for selection; enhancement of the binding of other monoclonal antibodies defining a denaturation-sensitive antigenic domain. It was shown that the natural immune response against certain functionally important, denaturation-resistant immunogenic domains on the native protein can be closely mimicked by immunization with defined protein fragments. Antigenic sites present on these fragments may therefore represent essential constituents of a synthetic vaccine. The fine specificities of antibody populations in anti-peptide or anti-protein immune sera were analysed on the basis of single antigenic determinants by blocking assays using radiolabelled monoclonal antibodies that define eight distinct epitopes on the TBE virus glycoprotein. Quantitative differences in the blocking of certain monoclonal antibodies were also observed between human convalescent sera. The establishment of

such blocking profiles using a panel of well-characterized monoclonal antibodies may represent a general method for dissecting the specificities of antibody populations present in polyclonal immune sera and could allow investigations on determinant-restricted differences of immune responses and its possible implications for the course of the disease.

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1: Virology 1983 Oct 30;130(2):485-501 Related Articles, Books

Location of immunodominant antigenic determinants on fragments of the tick-borne encephalitis virus glycoprotein: evidence for two different mechanisms by which antibodies mediate neutralization and hemagglutination inhibition.

Heinz FX, Berger R, Tuma W, Kunz C.

A model showing the topological distribution, functions, and serological specificities of eight distinct, monoclonal antibody-defined epitopes on the tick-borne encephalitis (TBE) virus glycoprotein has been presented in a previous publication (F. X. Heinz, R. Berger, W. Tuma, and Ch. Kunz (1983). Virology 126, 525-537.) In the present report the influence of conformational change, chemical modification, and fragmentation on the antigenic reactivity of each epitope has been analyzed by the use of blocking enzyme immunoassays and "Western blotting." One of the two major antigenic domains (A), composed of three different epitopes, completely lost its antigenicity upon incubation at pH 5.0 or by treatment with guanidine-HCl/urea, SDS, reduction and carboxymethylation, as well as by proteolytic (trypsin, alpha-chymotrypsin, thermolysin) and chemical (CNBr) fragmentation. The second major antigenic domain (B), however, defined by four distinct monoclonal antibodies, three of which are hemagglutination (HA)-inhibiting, neutralizing, and protective, was shown to be resistant to

low pH, guanidine-HCl/urea treatment, and proteolytic cleavage of the native protein. Also, polyclonal immune sera from mice and rabbits contained antibody populations reactive with antigenic determinants which are resistant and others which are sensitive to conformational change and fragmentation. Glycoprotein fragments with molecular weights of about 9000, generated by proteolysis of the native protein, were immunoreactive with neutralizing and protective monoclonal antibodies (defining domain B) as well as with a polyclonal mouse immune serum. Thus, these fragments appear to contain antigenic determinants which are immunodominant on the native protein and play an important role in the induction of a protective immune response against TBE virus. In addition, these results show that antibody binding to antigenic domains which are topologically and structurally completely unrelated may result in neutralization and/or HA inhibition. As the presence of two receptor-binding sites is unlikely, different effector mechanisms may account for the effects of these antibodies. The antigenic reactivity of domain A is sensitive to the same treatments which also inactivate HA activity of TBE virus, whereas domain B is resistant. These treatments include a change of domain A induced by incubation at slightly acidic pH which also results in inactivation of virus infectivity. Antibodies to domain A therefore presumably block viral activities by direct binding at or near the putative receptor-binding site whereas antibodies to domain B may cause loss of biological activities by inducing a conformational change of the receptor-binding site.

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